



Risk of Breast Cancer Classified by Joint Estrogen Receptor and Progesterone Receptor Status among Women 20–44 Years of Age

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To gain insight into whether breast cancer tumors jointly classified by estrogen receptor (ER) and progesterone receptor (PR) status represent diseases with differing etiologies, data from a population-based case-control study of US women 20–44 years of age were analyzed. Cases included 1,556 women diagnosed between 1990 and 1992. Age- and geographic-frequency-matched controls included 1,397 women identified by random digit dialing. Heterogeneity between ER+PR+ and ER–PR– tumors was most pronounced in relation to age, race, and recreational exercise at 12–13 years of age. Multivariate-adjusted odds ratios for ER+PR+ tumors were 0.64 (95% confidence interval (CI): 0.47, 0.89) for 30–34 versus 40–44 years of age, 0.89 (95% CI: 0.63, 1.25) for Black versus White race, and 0.84 (95% CI: 0.68, 1.03) for exercise at 12–13 years of age above versus at or below the median. Corresponding odds ratios for ER–PR– tumors were 1.24 (95% CI: 0.86, 1.77), 1.51 (95% CI: 1.07, 2.14), and 1.15 (95% CI: 0.90, 1.48). Risk of ER–PR– cancer in relation to menstrual and reproductive (parity and lactation) characteristics, alcohol consumption, and family history of breast cancer was similar to that observed for ER+PR+ tumors. These findings only modestly support the hypothesis that hormonally related risk factors have differing relations with ER+PR+ versus ER–PR– tumors among younger women. *Am J Epidemiol* 2002;156:507–16.

breast neoplasms; case-control studies; receptors, estrogen; receptors, progesterone; risk factors

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; WHR, waist-to-hip ratio.

Ovarian hormones, primarily estrogen, are believed to play a role in breast cancer etiology (1, 2). The action of estrogen and progesterone on breast cell proliferation appears to be mediated by the estrogen receptor (ER) and progesterone receptor (PR) (3). Survival and response to hormonal therapy are most favorable among women diagnosed with tumors positive for both the ER and PR, interme-

diate for tumors discordant on receptor status (ER+PR–, ER–PR+), and least favorable for tumors negative for both receptors (4–6).

Clinical implications of tumor hormone receptor status have prompted investigators to examine whether risk factors for breast cancer vary by hormone receptor status (7). Epidemiologic studies examining hormone-related breast cancer

risk factors in relation to either the ER or PR status of the tumors have consistently shown that the ER+ tumor risk is positively associated with older age, White (vs. Black) race, and nulliparity (7, 8). More recent research has focused on determining whether the etiologies of breast cancer tumors classified by joint ER/PR status differ, with the assumption that ER+PR+ tumors are more hormonally sensitive (9–16).

Previous studies reported that risk of ER+PR+ breast cancer is positively associated with nulliparity, a later age at first birth, a later age at menarche, and a higher body mass index (BMI; weight in kg/height in m²), but that these factors were inversely related to the risk of ER–PR– tumors (9, 10, 12–15). These observations suggest that tumors subclassified by joint steroid receptor status may actually represent distinct forms of breast cancer with differing etiologies. A recent international comparison of age-specific breast cancer incidence rates by hormone receptor status led Yasui and Potter (17) to hypothesize that hormone-related factors associated with a western lifestyle may be more strongly related to ER+PR+ breast cancer than to other tumor subtypes and that these associations may vary by menopausal status. The Carolina Breast Cancer Study additionally explored whether the heterogeneity among tumor subtypes varied by menopausal status (14). Among premenopausal women, a high waist-to-hip ratio (WHR) was associated with an elevated risk of ER+PR+ tumors, but WHR was unrelated to ER–PR– tumor risk. Neither a family history of breast or ovarian cancer nor medical radiation exposure to the chest was related to ER+PR+ tumors, yet both factors increased ER–PR– tumor risk. Because of the limited number of premenopausal women in previous studies (13–15), data from a large group of mostly premenopausal women were analyzed to examine whether breast cancer risk factors were associated with and varied according to tumor types subclassified by joint hormone receptor status.

MATERIALS AND METHODS

Study population

The Women's Interview Study of Health was undertaken primarily to evaluate whether long-term oral contraceptive use, alcohol consumption, or adolescent diet was associated with breast cancer risk in young women. Methods have been described previously (18). In this population, an increased breast cancer risk was noted for women who were oral contraceptive users or alcohol drinkers as well as for those who had had a late age at first birth, an early age at menarche, a previous breast biopsy, a first-degree relative with breast cancer, or a low BMI (18–23). Breast cancer risk was not positively associated with WHR, cigarette smoking, miscarriages, or electric blanket use and was not inversely associated with recreational exercise (18, 20, 24–26).

Eligible women were 20–44 years of age and were residents of either the metropolitan area of Atlanta, Georgia; the three-county area surrounding Seattle, Washington; or one of five central New Jersey counties. Cases were newly diagnosed, between May 1, 1990, and December 31, 1992, with either in situ or invasive breast cancer. In this population,

risk factor profiles for in situ and invasive cases were found to be similar (27). Controls were identified by using the modified Waksberg's method of random digit dialing (28) and were frequency matched to the expected case distribution by 5-year age group and geographic site. Relevant institutional review boards approved all protocols.

In-person interviews were completed by 1,668 breast cancer cases (85.7 percent), with subject and physician refusals (6.6 and 5.8 percent, respectively) the primary reasons for nonparticipation. Subsequently, two cases were found to be ineligible. A total of 1,505 controls (78.7 percent of those selected) participated in the interview; subject refusal was the primary reason for nonparticipation (12.9 percent). The overall response rate for controls was 71.2 percent (random digit dialing screener response rate multiplied by interview response rate). Cases who did not have a telephone ($n = 21$) and controls previously diagnosed with in situ or invasive breast cancer ($n = 4$) were excluded to maintain case-control comparability.

Data collection

Signed informed consent was obtained. A structured questionnaire (average administration time, 70 minutes) was used to collect information on sociodemographic factors, reproductive and menstrual histories, hormone use, alcohol consumption, cigarette smoking, recreational exercise, medical history, and family history of breast cancer. Interviewers measured height, weight, and waist and hip circumferences (20). For cases, ER and PR status (classified as positive, borderline, negative, or unknown) as well as stage and grade of disease were either obtained from Surveillance, Epidemiology, and End Results (SEER) reports (Atlanta and Seattle) or abstracted from medical records in a manner compatible with SEER protocols (New Jersey).

Data analysis

Tumors for which hormone receptor status was borderline (ER, 2.7 percent; PR, 1.3 percent) were coded as receptor positive (10). Breast cancers were characterized by their joint ER and PR status (ER+PR+, ER+PR–, ER–PR+, ER–PR–, or ER/PR unavailable when either receptor status was unknown).

Chi-square tests were used to determine whether risk factors were associated with tumors classified by joint receptor status as well as with the availability of receptor information (29). Unordered polytomous logistic regression (SAS PROC CATMOD; SAS Institute, Inc., Cary, North Carolina) was used to determine odds ratios and 95 percent confidence intervals for each joint steroid receptor subgroup compared with the same control group (30). In addition to providing information on etiologic inference, this technique identifies sources of heterogeneity between tumor subgroups.

Estimates were adjusted for age and geographic site (hereafter referred to as the age- and center-adjusted model). Joint receptor breast cancer risk was examined in relation to the following characteristics believed to influence risk via a hormonal pathway: BMI at interview and at 20 years of age, WHR, age at menarche, menopausal status (postmenopause

defined as no menstrual period for at least 6 months prior to a case's diagnosis date and to a control's random digit dialing identification date), gravidity, abortion or miscarriage, parity, age at first birth, lactation, oral contraceptive use, years since last oral contraceptive use, cigarette smoking, usual alcohol intake, and moderate and vigorous exercise at three time periods (12–13 years of age, 20 years of age, year prior to interview) as well as the average of these three time periods (24). Family (mother or sister) history of breast cancer, education (high school or less/post-high school but no college degree/at least a college graduate), and race (White/Black) were also examined. The 89 cases and 104 controls whose race/ethnicity was unknown or who reported a racial/ethnic background for which there were too few women to enable meaningful analyses were excluded from further consideration. Thus, 1,556 cases and 1,397 controls were available for analysis.

After a thorough examination of characteristics measured on a continuous scale, cutpoints were selected to capture the underlying relation with the fewest categories needed to maximize the stability of estimates. Covariates were entered as indicator variables, and, in general, continuous variables were dichotomized at the median by using the distribution of controls. Subjects for whom values for a variable were missing were excluded from any analyses pertaining to that variable.

Pairwise differences between regression coefficients among the steroid-receptor case subgroups for a risk factor were assessed by using a Wald chi-square statistic (31). Incorporating the covariance between parameter estimates from the polytomous model into the chi-square statistic provides a more powerful comparison of the coefficients than does a chi-square statistic based on separate logistic models, where the covariance is assumed to be zero (31).

To determine whether confounding accounted for the associations observed in the age- and center-adjusted models, all characteristics for which risk estimates were significant, along with age and geographic site, were simultaneously included in a single model (hereafter referred to as the multivariate-adjusted model). This latter model also included risk factors found to have statistically significantly different regression coefficients among steroid receptor subgroups. Estimates from other models, including one containing all of the breast cancer risk factors under consideration, regardless of significance, as well as a model with just the risk factors that were found to have risk estimates that differed significantly between steroid receptor subgroups, were not materially different (data not shown). To adjust for stage of disease, case-only models were fit. In these models, each receptor subgroup was compared with the ER+PR+ subgroup.

RESULTS

Hormone receptor status was unavailable for 22 percent of the cases (table 1). Compared with women who resided in either of the other sites or those who were older, women who resided in New Jersey or those who were younger were slightly more likely to have steroid receptor information available. The proportion of Black women and White

women with receptor information available was similar (81 and 77 percent, respectively). Although family income was statistically significantly associated with steroid receptor status availability, women whose family income was above and below the middle \$35,000–\$49,999 category were equally likely to have such information available and were more likely to have this information than were women in this middle category. For 20 percent of women with in situ versus 90 percent of women with distant tumors, receptor status was known. Among in situ cases, women with and without ER/PR information did not differ regarding age, education, or income (data not shown). Women with grade I tumors were significantly less likely to have hormone receptor information available than were women with grade IV tumors. None of the other variables examined, including the hormonal or lifestyle characteristics, was associated with the availability of ER/PR status (data not shown).

Table 2 shows the distribution of the joint hormone receptor status of the breast cancer tumors as well as their distribution stratified by cases' age and race. Of the 78 percent of cases for whom ER/PR status was known, 51, 10, 10, and 30 percent of the tumors were classified as ER+PR+, ER+PR–, ER–PR+, and ER–PR–, respectively. Both age and race were associated with joint hormone receptor status ($p < 0.01$). As age increased, the proportion of women with ER+PR+ tumors increased, and this finding corresponded primarily with a decline in the proportion of women diagnosed as having ER–PR– tumors. Relative to Black women, White women were almost 1.5 times more likely to have ER+PR+ tumors (34 and 54 percent, respectively) but only 60 percent as likely to have ER–PR– tumors (43 and 27 percent, respectively).

In the age- and center-adjusted models, associations between hormone-receptor-subclassified breast cancer tumors and gravidity, previous history of abortion or miscarriage, BMI at 20 years of age, and recreational exercise at 20 years of age, as well as average recreational exercise, were in the expected directions to those previously observed for breast cancer, yet the confidence intervals were wide (data not shown). Heterogeneity among the steroid receptor subgroups in their associations with these risk factors was not apparent. Thus, these factors were not considered further. Risk estimates in the multivariate-adjusted model (table 3) were similar to those observed in the age- and center-adjusted models. Overall, multivariate adjustment resulted in small changes (<10 percent) in the magnitude of the odds ratios that tended toward the null value. Age- and center-adjusted associations for WHR, age at first birth, alcohol consumption, and recreational exercise at 12–13 years of age were attenuated following multivariate adjustment.

Associations observed for ER+PR+ tumors were similar to those generally reported for breast cancer risk when hormone receptor status is not considered (table 3). Risk of developing ER+PR+ tumors was elevated if women were older, had a BMI below the median, were younger at menarche, had a family history of breast cancer, or were premenopausal. Furthermore, White race, higher education (at least a college degree), nulliparity, later age at first birth, never lactating, and greater consumption of alcohol (≥ 7

TABLE 1. Distribution of the availability of steroid receptor information, by selected characteristics, among women breast cancer cases 20–44 years of age in Atlanta, Georgia; New Jersey; and Seattle, Washington, 1990–1992

	Information available		Information not available		χ^2 p value
	No.	%	No.	%	
All cases	1,212	78	344	22	
Geographic site					
Atlanta	380	77	113	23	
New Jersey	396	82	86	18	
Seattle	436	75	145	25	0.02
Age (years in tertiles)					
20–29	44	79	12	21	
30–34	163	84	30	16	
35–39	367	79	95	21	
40–44	638	76	207	24	0.04
Race					
White	1,004	77	296	23	
Black	208	81	48	19	0.16
Education					
≤High school	310	76	97	24	
Post-high school	421	80	107	20	
≥College graduate	481	77	140	23	0.40
Family income (\$)*					
<15,000	98	80	25	20	
15,000–24,999	125	81	30	19	
25,000–34,999	161	82	35	18	
35,000–49,999	193	70	84	30	
50,000–69,999	260	79	70	21	
70,000–89,999	161	78	46	22	
≥90,000	191	79	50	21	0.03
Tumor stage†					
In situ	43	20	175	80	
Local	625	85	110	15	
Regional	497	91	47	9	
Distant	26	90	3	10	<0.0001
Tumor grade‡					
I	37	76	12	24	
II	168	83	34	17	
III	325	92	28	8	
IV	77	97	2	3	<0.0001

* Family income was missing for 23 and 4 women for whom receptor status was and was not available, respectively.

† Tumor stage was missing for 21 and 9 women for whom receptor status was and was not available, respectively.

‡ Tumor grade information was not available for New Jersey women; additionally, grade was missing for 209 and 181 women for whom receptor status was and was not available, respectively.

drinks per week) were also related, but nonsignificantly, to an increased risk of ER+PR+ tumors.

Many of the odds ratios estimating the association for hormonal (age, WHR, current cigarette smoking, and recre-

TABLE 2. Distribution of joint estrogen receptor and progesterone receptor status among 1,556 women breast cancer cases 20–44 years of age in Atlanta, Georgia; New Jersey; and Seattle, Washington, 1990–1992

	Receptor status available								Receptor status not available	
	ER*+PR*+		ER+PR–		ER–PR+		ER–PR–		No.	%‡
	No.	%†	No.	%†	No.	%†	No.	%†		
All cases	616	51	118	10	118	10	360	30	344	22
Age (years)										
20–29	14	32	5	11	7	16	18	41	12	21
30–34	68	42	24	15	13	8	58	36	30	16
35–39	186	51	33	9	37	10	111	30	95	21
40–44	348	55	56	9	61	10	173	27	207	24
Race										
White	546	54	94	9	93	9	271	27	296	23
Black	70	34	24	12	25	12	89	43	48	19

* ER, estrogen receptor; PR, progesterone receptor.

† Percentage of cases whose hormone receptor status was known.

‡ Percentage of total cases (available + not available hormone receptor status).

ational exercise at 12–13 years of age and during the year prior to interview) and sociodemographic (race and education) characteristics in relation to ER–PR– tumors were in the opposite direction of the risk estimates observed for ER+PR+ tumors, albeit in some instances risk estimates were extremely close to the null value. Heterogeneity was most pronounced between the ER+PR+ and ER–PR– beta coefficients for age (30–34 vs. 40–44 years), race, and recreational exercise at 12–13 years of age.

Age at menarche, menopausal status, alcohol consumption, and family history of breast cancer similarly influence breast cancer risk, regardless of tumor steroid subtype. Nulliparous women were at increased risk of all tumor types except ER–PR+. An inverse association was observed between months of lactation and each of the hormone receptor tumor subtypes, with the strongest risk reduction observed for ER+PR– tumors (multivariate-adjusted odds ratio = 0.29, 95 percent confidence interval (CI): 0.13, 0.66). Finally, ever use of oral contraceptives was only modestly associated with an elevated risk of both ER– tumor types but neither ER+ tumor type. When time since last oral contraceptive use was explored, risk was highest for women who used them during the 5-year interval prior to interview. However, the magnitude of the association was actually the weakest for ER+PR+ tumors; the age- and center-adjusted odds ratios for oral contraceptive use within the 5 years prior to interview versus never use of oral contraceptives were 1.33 (95 percent CI: 0.95, 1.86), 1.82 (95 percent CI: 0.96, 3.45), 2.40 (95 percent CI: 1.17, 4.94), and 1.72 (95 percent CI: 1.14, 2.60) for ER+PR+, ER+PR–, ER–PR+, and ER–PR– tumors, respectively.

Associations for the risk factors examined in relation to the discordant receptor tumors (ER+PR– or ER–PR+) were not

consistently more similar to those observed for either ER+PR+ or ER–PR– tumors. In addition, the beta coefficient for ER+PR– in relation to several risk factors differed from the beta coefficients for the other tumor subtypes; however, no clear pattern emerged. Since fewer women were diagnosed with the discordant tumors, our ability to compare these two subgroups with one another as well as with ER+PR+ and ER–PR– tumors was limited. Associations for unclassified tumors differed from those observed for the other tumor subgroups regarding the women's age, education, WHR, lactation, and exercise at 12–13 years of age. These findings are difficult to interpret since unclassified tumors are a mixed group of hormone receptor tumor subtypes.

Analyses restricted to premenopausal women (88 percent of the population) as well as analyses reconducted by excluding women with in situ (14 percent) and unknown-stage (2 percent) tumors yielded results essentially unchanged from those presented in table 3 (data not shown). Adjustment for tumor stage in case-only models did not materially modify the risk estimates obtained from unadjusted models (data not shown). Because of the previously noted association between race and tumor steroid subtype (32, 33), estimates with (table 3) and without (data not shown) adjustment for race were compared. In general, risk estimates were similar in the two models; however, with adjustment for race, the difference between the ER+PR+ and ER–PR– tumors' beta coefficients for parity and age at first birth no longer remained. Small stratum-specific sample size prevented a formal evaluation for interaction, but examination of the odds ratios did not suggest an interaction between race and either of these reproductive factors (data not shown).

TABLE 3. Multivariate-adjusted* odds ratios and 95% confidence intervals for the association between risk factors and breast cancer risk, by steroid receptor subtype, among women 20–44 years of age in Atlanta, Georgia; New Jersey; and Seattle, Washington, 1990–1992

	No. of controls	A†: ER+PR+			B: ER+PR–			C: ER–PR+			D: ER–PR–			E: Not available		
		No.	OR‡	95% CI‡	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Age (years)																
20–29	58	14	0.80	0.64, 1.01	5	0.86	0.53, 1.39	7	1.00	0.64, 1.57	18	^E 1.03	0.78, 1.38	12	^D 0.69	0.52, 0.92
30–34	210	68	^{B,D} 0.64	0.47, 0.89	24	^{A,E} 1.37	0.80, 2.34	13	0.66	0.33, 1.31	58	^{A,E} 1.24	0.86, 1.77	30	^{B,D} 0.46	0.29, 0.71
35–39	441	186	0.49	0.26, 0.93	33	0.92	0.33, 2.54	37	1.37	0.53, 3.53	111	0.97	0.51, 1.88	95	0.64	0.32, 1.27
40–44	688	348	1.00		56	1.00		61	1.00		173	1.00		207	1.00	
Race																
White	1,180	546	1.00		94	1.00		93	1.00		271	1.00		296	1.00	
Black	217	70	^D 0.89	0.63, 1.25	24	1.33	0.75, 2.37	25	1.55	0.87, 2.74	89	^A 1.51	1.07, 2.14	48	1.06	0.72, 1.58
Education																
≤High school	347	146	1.00		25	1.00		35	1.00		104	1.00		97	1.00	
Post–high school	508	190	0.89	0.68, 1.17	44	1.10	0.64, 1.88	45	0.88	0.54, 1.44	142	0.95	0.70, 1.29	107	0.70	0.50, 0.96
≥College graduate	515	280	^E 1.22	0.92, 1.62	49	1.07	0.61, 1.90	38	0.68	0.38, 1.19	114	0.81	0.57, 1.15	140	^A 0.79	0.56, 1.12
Body mass index (weight in kg/ height in m ² ; median)																
≤24.6	642	351	1.00		58	1.00		50	1.00		168	1.00		183	1.00	
>24.6	660	249	0.77	0.62, 0.96	56	1.04	0.68, 1.60	61	1.01	0.66, 1.56	176	0.91	0.70, 1.19	153	0.90	0.69, 1.18
Waist-to-hip ratio (median)																
≤0.92	683	342	1.00		65	1.00		49	1.00		170	1.00		199	1.00	
>0.92	644	261	0.90	0.73, 1.11	51	0.91	0.60, 1.38	63	^E 1.28	0.84, 1.95	178	1.07	0.83, 1.38	137	^C 0.78	0.60, 1.01
Parity																
Ever	1,086	467	1.00		84	1.00		95	1.00		276	1.00		248	1.00	
Never	311	148	1.20	0.87, 1.68	34	1.80	0.95, 3.41	23	1.03	0.53, 1.99	84	1.22	0.81, 1.82	96	1.89	1.26, 2.83
Age at first birth (years; median)																
≤24.3	550	193	1.00		32	1.00		43	1.00		147	1.00		106	1.00	
>24.3	536	274	1.21	0.94, 1.57	52	1.69	0.99, 2.86	52	1.43	0.87, 2.35	129	1.03	0.75, 1.41	141	1.34	0.96, 1.85
Lactation (months; lowest 75th vs. upper 25th percentile)																
Never	421	177	1.00		35	1.00		39	1.00		131	1.00		100	1.00	
≤12	419	191	0.99	0.76, 1.30	40	0.87	0.52, 1.46	40	1.15	0.69, 1.90	94	0.78	0.57, 1.08	92	0.90	0.64, 1.26
>12	246	99	^B 0.80	0.58, 1.12	9	^{A,C,D,E} 0.29	0.13, 0.66	16	^B 0.82	0.43, 1.59	51	^B 0.75	0.50, 1.12	56	^B 0.81	0.54, 1.22
Oral contraceptive use																
Never	215	87	1.00		17	1.00		9	1.00		44	1.00		48	1.00	
Ever	1,182	529	1.15	0.86, 1.54	101	1.16	0.65, 2.06	109	2.02	0.98, 4.14	316	1.46	1.00, 2.14	296	1.13	0.79, 1.62
Cigarette smoking																
Never	743	318	1.00		78	1.00		66	1.00		191	1.00		192	1.00	
Former	299	144	0.99	0.77, 1.28	23	0.76	0.45, 1.27	23	0.94	0.56, 1.58	80	1.02	0.75, 1.41	81	1.02	0.74, 1.39
Current	351	154	^B 1.11	0.86, 1.44	17	^A 0.48	0.27, 0.86	29	0.86	0.52, 1.42	89	0.89	0.65, 1.21	71	0.81	0.58, 1.12

Usual alcohol intake (drinks/week)															
Nondrinker	503	187	1.00		45	1.00		44	1.00		124	1.00		117	1.00
<7	729	342	1.11	0.88, 1.41	58	0.86	0.55, 1.35	52	0.87	0.55, 1.39	180	1.08	0.81, 1.43	182	0.95 0.71, 1.26
≥7	161	86	1.33	0.94, 1.87	14	0.94	0.47, 1.86	22	1.64	0.90, 2.98	56	1.38	0.93, 2.06	45	1.02 0.66, 1.55
Recreational exercise at 12–13 years of age (relative units/week)															
≤47.5	728	359	1.00		59	1.00		66	1.00		171	1.00		197	1.00
>47.5	669	257	^D 0.84	0.68, 1.03	59	0.95	0.64, 1.42	52	0.87	0.58, 1.30	189	^{A,E} 1.15	0.90, 1.48	147	^D 0.83 0.65, 1.07
Recreational exercise in year prior to interview (relative units/week)															
≤13.5	722	292	1.00		46	1.00		70	1.00		199	1.00		170	1.00
>13.5	675	324	1.12	0.91, 1.37	72	^{C,D} 1.60	1.06, 2.40	48	^B 0.84	0.55, 1.26	161	^B 0.88	0.68, 1.12	173	1.04 0.81, 1.34
Age at menarche (years)															
≤12	711	343	1.00		61	1.00		65	1.00		202	1.00		190	1.00
≥13	685	272	0.77	0.63, 0.94	57	0.93	0.63, 1.38	53	0.87	0.58, 1.30	158	0.78	0.61, 1.00	153	0.81 0.63, 1.04
Family history of breast cancer															
Never	1,304	525	1.00		106	1.00		104	1.00		306	1.00		288	1.00
Ever	93	91	2.31	1.67, 3.18	12	1.69	0.89, 3.22	14	1.93	1.03, 3.61	54	2.53	1.74, 3.69	56	2.63 1.81, 3.82
Menopausal status															
Premenopausal	1,210	559	1.00		107	1.00		107	1.00		317	1.00		305	1.00
Postmenopausal	182	56	0.66	0.46, 0.93	11	0.77	0.39, 1.53	11	0.65	0.33, 1.29	42	0.78	0.52, 1.15	39	0.70 0.47, 1.06

* Estimates were simultaneously adjusted for all of the other factors in the table as well as for study site.

† The five letter column headings (A–E) are used as superscripts in the body of the table to indicate statistically significant differences between steroid receptor subtype-specific estimates.

‡ ER, estrogen receptor; PR, progesterone receptor; OR, odds ratio; CI, confidence interval.

DISCUSSION

Even given our study population's restricted age range, age was inversely related to the proportion of ER-PR- tumors but positively associated with the proportion of ER+PR+ tumors. The increased proportion of ER+PR+ breast cancer tumors for successive age categories concurs with prior reports (11, 17). Others have also noted a higher proportion of ER+PR+ tumors but a lower proportion of ER-PR- tumors in Whites versus Blacks (34).

Our study's findings provide weak support for the hypothesis promulgated by Potter et al. (10, 17): ER+PR+ and ER-PR- breast cancer tumors have different risk factor profiles. In our study, the strongest evidence supporting this hypothesis, although limited, was that the regression coefficients for ER+PR+ and ER-PR- tumors were different for age, race, and exercise at 12-13 years of age. Other evidence for differences in risk factor profiles is provided by several characteristics (age, WHR, current cigarette smoking, and recreational exercise at 12-13 years of age and during the year prior to interview), with risk estimates in opposite directions for the two tumor subtypes. On the other hand, the lack of heterogeneity among tumor subgroups for many of the reproductive and menstrual characteristics commonly considered to influence breast cancer risk through a hormonally mediated pathway provides little support for this hypothesis (35). Failure to provide stronger support may be due to the limited power of our study to detect such subtle subgroup heterogeneity.

If tumors classified by their joint hormone receptor status represent different stages of the same disease, then control for stage and tumor size would be expected to influence the observed associations. Risk estimates remained essentially unchanged in analyses considering tumor stage, providing additional support for the hypothesis that tumors of differing steroid receptor statuses may be etiologically distinct. Tumor size was not examined because of concerns about the reliability of these data. Earlier studies adjusting for tumor stage (14) or size (10) found that these characteristics did not influence risk estimates.

Our findings do not agree with previous reports of stronger associations for ER+PR+ tumors and hormone-related characteristics (9, 10, 12-15). Inconsistency may reflect differences in study design or populations. Breast cancer risk factors and the underlying biologic mechanisms may vary with menopausal status (14, 36). The discussion therefore focuses on comparing our results with those of other studies that included premenopausal women, since our population was 88 percent premenopausal.

Our finding of a reduced risk of ER+PR+ tumors among women with a higher BMI is consistent with one (14) but not the other (15) known study of premenopausal women. In studies of premenopausal breast cancer risk that do not consider hormone receptor subtype, an inverse or even no association is often observed for BMI (37-40). Premenopausal obesity has been associated with menstrual cycle irregularities resulting in lower estrogen and progesterone levels, which may lower breast cancer risk (38). Abdominal fat is considered more metabolically active than peripheral fat (41). Central fat has been associated with increased

estrogen and testosterone levels but decreased sex hormone-binding globulin levels (38). Additionally, it has also been linked with insulin resistance, which may in turn be associated with an elevated breast cancer risk (42). However, we did not observe an association between WHR and any of the hormone receptor subgroups. This finding contrasts with the previous report of a twofold risk of ER+PR+ breast cancer tumors in relation to a higher WHR (14) as well as with two recent studies not considering hormone receptor status that observed positive associations between WHR and premenopausal breast cancer risk (43, 44).

As observed in the Carolina Breast Cancer Study, we found that nulliparous women were at increased risk of ER+PR+ tumors (14). In contrast, nulliparous women were also at increased risk of ER-PR- tumors in our study but not in the Carolina Breast Cancer Study. In addition, the increased ER+PR+ tumor risk for older versus younger age at first birth that we noted is not consistent with the null association reported in the Carolina Breast Cancer Study (14). A later versus earlier age at first birth has been hypothesized to increase breast cancer risk since pregnancy-related increases in estrogen and progesterone levels (45) are not offset by the benefits associated with an earlier age at breast cell differentiation (46).

Physical activity has been hypothesized to reduce breast cancer risk by a variety of mechanisms, including an influence on menstrual cycle (47, 48) or body size characteristics (37). A reduced risk of ER+PR+ tumors was observed in these data for higher levels of participation in recreational exercise at 12-13 years of age but not for exercise in the year prior to the interview. In a previous population-based case-control study conducted in Los Angeles, California, an inverse association between lifetime recreational physical activity levels and all steroid receptor tumor subgroups except ER-PR+ was observed among premenopausal women (15). Explanations for our observation of an increased risk of ER+PR- tumors in relation to recreational exercise in the year prior to interview is unclear and may have been due to chance.

Unlike the premenopausal findings from the Carolina Breast Cancer Study (14), we observed no differences in ER+PR+ and ER-PR- tumors in relation to cases' age at menarche, ever/never oral contraceptive use, and family history of breast cancer. Our finding of a nonsignificant elevated risk across all hormone receptor status subgroups, except for ER+PR- tumors, in relation to higher consumption of alcoholic drinks also disagreed with the null findings (13) and the nonsignificant reductions in risk (14) observed in the two known previous studies of premenopausal women. As suggested previously (25), the strong decreased risk of ER+PR- breast cancer for current versus never cigarette smokers may have been a chance finding, particularly in light of the large number of comparisons we made. Finally, neither our results nor those of the Carolina Breast Cancer Study (14) support differences among these two breast tumor subgroups for a previous history of an abortion or miscarriage.

Bias must be considered when interpreting our findings. Response rates were higher among cases than controls. However, selection bias from control nonparticipation is

unlikely to explain our findings of heterogeneity among tumor subgroup associations with some, but not other, risk factors. Since each case group was compared with the same control group, any selection bias would be expected to similarly affect the estimates among the tumor subgroups. Most of the associations for ER+PR+ tumors were in the expected directions based on previous studies of breast cancer risk (35), and it is extremely unlikely that recall bias issues would apply to only those cases in a specific hormone receptor status subgroup. In contrast, our WHR findings were not in the expected direction. This unexpected finding may have been due to a higher refusal rate among heavier women who were invited to be controls. Data from this study suggest otherwise; no differences in self-reported weight were found between participants who completed the full study interview and those willing to complete only a short nonrespondent questionnaire (49).

Distributions of the breast cancer risk factors were generally similar for cases for whom hormone receptor status information was and was not available, which also argues against selection bias. Women with in situ and lower-grade tumors were more likely to have an unknown hormone receptor status than were women with other stage or grade tumors. In the study population from the Women's Interview Study of Health, associations for in situ versus regional/distant tumors differed for only nulliparity, BMI, and alcohol consumption (27). Excluding in situ or unknown-stage tumors did not modify the risk estimates shown in table 3.

Numerous laboratories determined ER and PR status, primarily by using the dextrose-charcoal-coated biochemical assay as opposed to immunohistochemical techniques. The higher prevalence of dextrose-charcoal-coated testing reflects the time period (1990–1992) in which this study was conducted. Despite generally high agreement between these two methods, differences in classification as well as interlaboratory variability may account for discrepancies among studies' findings (50). Although prediction of prognosis and response to hormonal treatment by hormone receptor status is relatively consistent, misclassification of hormone receptor status may make it more difficult to disentangle whether the more subtle etiologic relations vary among hormone receptor subgroups (50).

The methodological strengths of this study to examine whether associations differed according to tumor subgroups of steroid receptor status include analyses based on the largest known sample size of premenopausal women to date. However, subgroup analyses undertaken in this study were hindered by decreased power to detect associations of small magnitude. Other study strengths include the population-based design, the wide range of breast cancer risk factors available for analyses, and the use of a standardized anthropometric protocol. In general, our findings did not strongly support the notion that many of the established or suspected hormonal breast cancer risk factors differ regarding their relations with ER+PR+ versus ER–PR– breast cancer tumors in younger women.

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